REMARKS

The August 27, 2002 Official Action and the single reference cited therein have been carefully considered. In view of the amendments presented herewith in the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset, it is noted that a shortened statutory period of three months was set forth in the August 27, 2002 Official Action. The initial due date for response, therefore, was November 27, 2002. A petition for a two (2) month extension of the response period is presented with this Amendment and Request for Reconsideration, which is being filed within the one month extension period.

In the August 27, 2002 Official Action, the 35 U.S.C. §102(b) rejection of claims 1-6, 8-13, 15-20 and 37 as allegedly anticipated by the disclosure of Graham et al. (WO 97/05280) has been repeated and made final, as has the 35 U.S.C. §103(a) rejection of claims 7 and 14, which are alleged to be obvious in view of Graham et al.

The above-mentioned rejections constitute all of the grounds set forth in the August 27, 2002 Official Action for refusing the present application.

In accordance with the present amendment, claim 1 has been amended to incorporate the subject matter of claims 2-4 and to include the recitation "and aggregation of said metal SER(R)S surface being dependent on the presence of said target nucleic

acid in said sample".

Support for the amendatory language added to claim 1 is provided in the originally filed application, as follows:

(i) "said metal surfaces...to which said sample is exposed", which appears in claims 1 (amended), subparagraph (a) lines 16-18, is based on original claim 2;

(ii) "at least two separate components", which appears in claim 1 (amended) subparagraph (a) lines 3 and 4, is based on original claim 3;

(iii) "including a first agent having a metal surface...thereby causing surface enhancement of a SAS associated with one or both of the metal surfaces", which appears in claim 1 (amended) subparagraph (a) lines 4-15, is based on original claim 4, as well as Fig. 3(c), which shows that the detection agent having nucleic acid probe X does not include a dye, whereas the detection agent having nucleic acid probe Y2 includes dye "C", which is detectable in the resulting complex showing the presence of the X' - Y_2' sequence in the sample; and

(iv) "aggregation of said metal SER(R)S surface being dependent on the presence of said target nucleic acid in said sample", which appears in claim 1 (amended) subparagraph (a) lines 19-21, has support at page 6, lines 1-12 and 24-27 of the present specification.

In view of the present amendment to claim 1, claims 2-4 have been canceled. Conforming amendments have also been made in claims 5 and 15, and claim 20 has also been canceled.

In view of the clear support for the present amendment in the application as originally filed, this amendment does not introduce new matter into the application.

Entry of the present amendment is respectfully requested, as it requires neither further examination nor search and is believed to place the application in condition for allowance. On the other hand, entry of the amendment should materially reduce the issues that would have to be considered on appeal, should an appeal be necessary in this case. This amendment was not presented earlier because the argument to which it primarily responds was presented for the first time in the August 27, 2002 Official Action. See page 8 of the August 27, 2002 Official Action. That is when it first became evident to applicants that the claims then pending were being interpreted by the Examiner in such a way that surface enhancement, via aggregation of metal SER(R)S surfaces, is not dependent on the presence of target nucleic acid in the sample.

For the reasons provided below, the prior art rejections maintained in the August 27, 2002 Official Action are respectfully traversed.

A. The 35 U.S.C. §102(b) Rejection of Claims 1-6, 8-13, 15-20 and 37 Cannot be Maintained because Graham et al. Fails to Identically Disclosure or Describe the Subject Matter of Those Claims

As originally presented and as now amended, applicants' claims expressly require that the metal surfaces are ineffective to cause surface enhancement in the form in which they are

present in the detection agent to which the sample is exposed. This aspect of applicants' invention was previously set forth in claim 2. Applicants have urged that this is a patentably significant feature of the present invention that distinguishes it from Graham et al. and remain convinced that this is so. See applicants' July 25, 2002 Amendment and Request for Reconsideration Under 37 C.F.R. §1.111 at 14.

As pointed out at page 23 of Graham et al., the SER(R)S-active surface "may be any suitable surface, usually metallic, which gives rise to enhancement of the Raman effect....", and is "preferably, an aggregation of metal colloidal particles". Furthermore, as disclosed at page 24, lines 12 and 13 of Graham et al., the colloidal metal particles are "aggregated immediately prior to use". Clearly, Graham et al. does not satisfy the requirement of the present invention that the metal surfaces are ineffective to cause surface enhancement in the form in which they are present in the detection agent to which the sample is exposed. Graham et al. neither teaches nor suggests this aspect of applicants' invention, notwithstanding the Examiner's contention to the contrary.

In order to further differentiate the present invention from Graham et al., claim 1 has been amended to specify that "aggregation of said metal SER(R)S surface [is] dependent on the presence of said target nucleic acid in said sample". The dependence of surface enhancement on the presence of target

nucleic acid in the sample is an inherent advantage of the method of the present invention because it dispenses with the need for separating unbound labeled detection agent from labeled target complexes. In other words, unbound label detection agent will not interfere with the reliable performance of the claimed detection method. This advantage is achieved, in accordance with this invention, precisely because the form in which the metal surface is present in the detection agent is ineffective to cause surface enhancement. See page 7, lines 10-21 of the present specification.

It is well settled that advantages accruing from the claimed method need not be recited, but must be considered in determining patentability. In re Estes, 164 U.S.P.Q. 5 519 (C.C.P.A. 1970). Nevertheless, in the interest of advancing prosecution in this case, claim 1 has been amended to specify that "aggregation of said metal SER(R)S surface [is] dependent on the presence of said target nucleic acid in said sample". The recitation of this particular feature of applicants' invention in the method of claim 1 should dispel any possible doubt that the claimed method is patentably distinguishable from Graham et al. There is clearly no teaching or suggestion of this aspect of applicants' invention in Graham et al.

For the above reasons, Graham et al. cannot reasonably be said to anticipate claims 1-6, 8-13, 15-20 and 37. Accordingly, the §102(b) rejection of claims 1-6, 8-13, 15-20 and 37 in view of Graham et al. is untenable and should be withdrawn.

B. The Disclosure of Graham et al. Fails to Render Obvious the Subject Matter of Claims 7 and 14

The rejection of claims 7 and 14 in view of Graham et al. cannot be maintained for at least the same reasons stated above with respect to the §102(b) rejection of claims 1-6, 8-13, 15-20 and 37 based on Graham et al.

As dependent claims, claims 7 and 14 must be held patentable over Graham et al. because the claims from which they depend are patentable over Graham et al. In re Fine, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988).

Accordingly, the 35 U.S.C. §103 rejection of claims 4 and 7 based on Graham et al. is improper and should be withdrawn.

In view of the present amendment and the foregoing remarks, all of the claims now pending are believed to be in condition for allowance. Therefore, the issuance of a Notice of Allowance is in order, and such action is earnestly solicited.

Respectfully submitted,

DANN DORFMAN HERRELL & SKILLMAN, P.C.

By: Patrick J. Hagan

Patrick J. Hagan
Registration No. 27,643

PJH:ksk

Marked-Up Copy of Amended Claims

1. (Twice Amended) A method for determining the presence or absence of a target nucleic acid sequence in a sample nucleic acid, the method comprising:

(a) exposing the sample to a detection agent comprising [a metal surface associated with a SER(R)S active species (SAS) and with a target binding species (TBS),] at least two separate components, including a first agent having a metal surface associated with a first target binding species (TBS) and a second agent having a metal surface associated with a second TBS, different from said first TBS, at least one of said metal surfaces being associated with a SER(R)S-active species (SAS), each of said first and second TBS being effective to bind to the target sequence, and wherein the binding of the first and second TBS to the target sequence causes aggregation of the metal surfaces associated with said TBS, thereby causing surface enhancement of a SAS associated with one or both of the metal surfaces, said metal surfaces being ineffective to cause surface enhancement in the form in which they are present in the detection agent to which said sample is exposed, and aggregation of said metal SER(R)S surface being dependent on the presence of said target nucleic acid in said sample; and,

(b) observing the sample/agent mixture using SER(R)S to detect any said surface enhancement [of the label,

wherein the binding of the TBS to the target sequence causes increased surface enhancement of the SAS].

5. (Thrice Amended) The method as claimed in claim 1 wherein [the] <u>each component of said</u> detection agent comprises monodisperse unaggregated colloidal metal particles associated with a TBS comprising a nucleic acid or nucleic acid analog which is complementary to all or part of the target sequence.

15. (Twice Amended) A method as claimed in claim 1 wherein more than one target sequence is determined using [multiple] detection [agents] <u>agent components</u> having distinguishable SAS.